BONE HEALTH IN YOUNG PATIENTS OF BREAST CANCER

This dissertation is submitted to

THE TAMILNADU

DR MGR MEDICAL UNIVERSITY,

*in partial fulfillment of the University regulations f*or

D. M (Medical Oncology)

Degree Examination of February 2008

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI – 600 020

FEBRUARY 2008

CERTIFICATE

This is to certify that the dissertation on **"BONE HEALTH IN YOUNG PATIENTS OF BREAST CANCER"** *is the bonafide work done by* ***Dr. NEELESH REDDY P.R,*** *in the department of Medical Oncology, College of Oncological Sciences, Adyar, Chennai, under my overall supervision and guidance, to my satisfaction.*

Place: Chennai
Date:

Dr. T. G. SAGAR, MD DM,
Professor and Head
Department of Medical Oncology,
College Of Oncological Sciences
Adyar, Chennai – 600 036.

ACKNOWLEDGEMENT

"Oh his lovable and selfless attitude
On his preliminary and priceless contribution
Emerge in my heart the tears of joy and gratitude
And I am indebted to HIM forever".

Words are too inadequate to express my gratitude, towards all the people who have been instrumental in guiding me in this dissertation. This effort would never have seen light of the day without their help.

I humbly record my deep sense of gratitude to ***Dr .T .G. Sagar****, MD, DM Professor and Head, Division of Medical Oncology, Cancer Institute (W.I.A) Adyar, Chennai for his constant support, encouragement and guidance during the course of this study. His profound knowledge in this field was crucial for this work. But for his unflinching confidence in me, it would have been an onerous task to complete this dissertation. I am deeply indebted to him.*

I express my sincere thanks and gratitude to ***Dr. Ganapathy Ramanan*** *M.D, DM. His ceaseless energy, guidance and leadership have always been a source of inspiration and support. I shall forever be thankful for his encouragement and advice, which gave me strength to complete this work.*

I extend my gratitude to ***Dr. Rejiv Rajendranath*** *MD, DM Assistant professor, Division of Medical Oncology, for his constructive criticism and support through out the study period.*

I extend my gratitude to ***Dr. Manjunath Doshetty*** *MD, for his concern, encouragement and advice during the period.*

I am greatly indebted to my parents, who have helped me constantly to reach this present stage. The role they have played in supporting me is beyond the reach of expression.

I sincerely thank all my colleagues and friends for their constant support and suggestions.

Last, but not the least; I thank all my patients for their kind co - operation in this study. May ***God Almighty*** *bestow upon them good health.*

CONTENTS

INTRODUCTION

INTRODUCTION

The incidence of breast cancer has been steadily increasing in India, keeping trend with global scenario, mostly contributed by the rapid economic development leading on to adoption of the western life styles. In a study by Yeole BB and Kurkure AP, there has been a significant leap in the incidence of breast cancer in India over the past two decades. Nearly 100,000 new cases of breast cancer are diagnosed in India every year and about 5% to 12% of them are young patients. At any given time there will be one million patients of breast cancer in India either on treatment or as survivors. The life time risk of developing breast cancer is 1:30 (incidence rate of 20 cases per 100,000) in Urban India and 1:65 (incidence rate of 8.6 cases per 100,000) in rural India, reflecting the influence of life style on breast cancer incidence[1, 55].

With the increase in awareness among general population, more and more patients present to their physicians at an early stage[1]. This along with the improvement in treatment modalities has resulted in an ever expanding population of breast cancer survivors, who are prone for long-term cancer treatment related complications including Poor Bone Health.

There has been a significant improvement in our knowledge regarding poor bone health among elderly subjects particularly, women at high risk[6], However there is still paucity of information about the status of bone health among young premenopausal females particularly in India. These patients who either have chemotherapy associated premature menopause or have been rendered estrogen deficient[2] (by castration) as a part of multimodal treatment, may be at a higher risk of osteoporosis and its complications.

This study is a sincere effort to determine the bone health of young survivors of breast cancer in India, so as to intervene at appropriate time and make a difference in their Quality Of Life.

AIM OF THE STUDY

AIM OF THE STUDY

The aim of the study is,

To study the Bone Mineral Density in young breast cancer patients and compare with matched controls.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

There has been increase in incidence of Breast Cancer World wide, and this combined with early detection and improvement in treatment modalities has resulted in significant improvement in survival of patients with breast cancer[1]. This ever expanding population of breast cancer survivors are increasingly prone for long-term treatment related complications.

***Impact on quality of life*:** One of the important long-term complications is significant bone loss, which entails an increased risk of fractures. As reported by Cooper C, the sites prone for fracture include neck of femur, vertebral spine particularly lumbar and radius among others[2]. These fractures are generally caused by trivial injury. Osteoporotic fractures drastically affect quality of life as are often associated with chronic pain and loss of mobility, making these patients dependent[3]. Ten to 20% of patients with fracture of neck of femur require long term hospital care after management of acute condition, while another 20% require assistance in coping with activities of daily living[4]. Similarly patients of fracture of spine have significant pain requiring significant medications as well as loss of work.

Therapy – induced damage to bone mass may rapidly become manifest, but it may also remain latent and become manifest later in life when it is supplemented

by the age dependent processes of bone loss. As found by Barr RD and Simpson T, this is particularly seen in young survivors, in whom the cancer treatment may have had a deleterious effect on acquisition of peak bone mass[5].

At present, most treating doctors including Medical Oncologists often see their patients at an advanced stage of poor bone health. This is unsatisfactory because the best treatment results can be achieved either by preventing the development of osteoporosis or in the early stage of disease[2].

Definition: Osteoporosis is defined as a reduction of bone mass (or density) or the presence of a fragility fracture. Loss of bone tissue causes deterioration in the architecture of the skeleton, the combination leading to a markedly increased risk or fracture[6].

***Operational definition*:** On conventional X-ray, osteoporosis can only be recognized with certainty when bone loss is around 30% to 50%[2]. Hence Osteoporosis has been increasingly defined in terms of bone density. Bone Mineral Density (BMD) measurements are usually given as Standard Deviation (SDs) from the mean. In relation to the bone mass of 30 yr old subjects of the same sex, this SD value is expressed as a T score and in relation to an age-matched population as Z-score[6-7].

A World Health Organization (WHO) expert panel proposed that a T score of – 2.5 SD below the young adult mean value be considered as Osteoporotic and those with T scores between – 1 and – 2.5 SD be considered as Osteopenic[2, 8].

Factors affecting bone integrity in breast cancer survivors[2, 9]

1. Hypogonadism
    a) Medical Castration.
    b) Surgical Oophorectomy.
    c) Radiocastration.
    d) Chemotherapy induced Ovarian Insufficiency.
2. Endocrine Manipulation.
3. Chemotherapy.

Mechanism of bone loss due to hypogonadism

In both sexes, the sex hormones play a fundamental role in maintaining bone mass. Menopause (natural or iatrogenic) is particularly vulnerable time during which women undergo an accelerated, transient phase of bone loss. This accounts for about 20% to 30% of cancellous bone loss and 5% to 10% of cortical bone loss. This accelerated phase can be fully prevented by early intervention before it merges with an underlying late phase of slow bone loss and proves to be detrimental[2].

Role of Estrogens: Estrogens act through direct and indirect mechanism to restrain bone resorption. The loss of this restraint in early menopause results in an increase in osteoclast formation and survival. At molecular level, estrogens interfere with the transcriptional regulation of a number of cytokines and cytokine-related factors that influence the differentiation of osteoclast progenitors and osteoclast survival, such as interleukin-1, interleukin-6, tumor necrosis factor and osteoprotegerin[10].

A pattern of bone loss similar to that seen after natural menopause also occurs in younger women with amenorrhoea caused by dysregulation of gonadotropin-releasing hormone (GnRH) and premature ovarian failure secondary to chemotherapy. Richelsen et al observed that Bone Mineral Density values in women who had been oophorectomized 20yrs earlier and in postmenopausal women who had been amenorrheic for a comparable period but were 20yrs older were similar and significantly lower than those in young, healthy premenopausal women[11]. Cann et al demonstrated that women with premature ovarian failure have an average vertebral bone density of 21% below that of age matched eumenorrheic women[12].

In addition estrogens play a vital role in achieving maximal bone mass during puberty. If gonadal dysfunction occurs during this time, peak bone mass is reduced and the person is susceptible to poor bone health later in life.

***Medical Oophorectomy*:** This is achieved by administration of Gonadotropin-releasing hormone agonist. GnRH analogs continually stimulate the gonadotropic cells in the pituitary, thus quickly leading to downregulation of the Luteinizing hormone-releasing hormone receptors and thus to complete ovarian insufficiency[2]. This form of endocrine manipulation is effectively tried in premenopausal women with breast cancer. Johansen J, et al, noted in their study that GnRH therapy is associated with a marked decline in spinal bone density just after 6 months of therapy[13]. However on a positive note, Fogelman I, et al reported that there will be atleast partial recovery of BMD after 1 year of cessation of GnRH therapy[14].

Surgical Oophorectomy: This method is for permanent and complete ablation of ovarian function. Though not popular in the west now with the use of medical oophorectomy, it is still the cost effective method followed at many oncological centres in developing countries.

Radiocastration: In few of the centres including Cancer Institute (WIA) radiotherapy is used for ablation of ovarian function in which 20 Gy of radiotherapy is delivered over a period of five days.

Chemotherapy induced ovarian insufficiency (hypogonadism): Ovarian insufficiency generally develops with in 1 year of therapy in 63% to 96% of premenopausal women with breast cancer who receive postoperative adjuvant

chemotherapy regimens, such as cyclophosphamide, methotrexate and flurouracil[15] or doxorubicin, cyclophosphamide and flurouracil protocols[2].

Cyclophosphamide: It is the major cause of hypogonadism in these patients as a result of primary ovarian failure. Correspondingly, there is an increase in plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH), indicating that chemotherapy affects the ovary itself and not the hypothalamus or pituitary. Adrenal function is also unaffected[15]. This has been confirmed by Charles LS, et al in their prospective study. The metabolite phosphoramide mustard is likely to be the culprit for ovarian toxicity of cyclophosphamide[16]. The dose of cyclophosphamide to cause permanent ovarian failure is dependent on age of patient. At 20yrs, 35yrs and 45 yrs the dose of cyclophosphamide to cause ovarian failure was 30gm, 10gm and 5gm respectively[56].

Pathogenesis: Studies in animals have shown that cyclophosphamide causes a dose dependent destruction of ovarian follicles and that primordial follicle are most sensitive, followed by antral and growing follicles[2]. Ataya K and Moghissi K proposed that, the Granulosa cells seem to be the primary ovarian target cells for cyclophosphamide. This effect involves alkylation of cell membrane and intracellular proteins and/or nuclear damage. Damage to the granulosa cells would affect the oocyte through the gap junctions known to connect the oocyte with its surrounding cumulus oophoricus granulosa cells[17].

Most of the patients receiving chemotherapy (that includes cyclophosphamide) become amenorrheic during or within 2 to 4 months after the end of the chemotherapy. As has been reported by Reichman BS, et al the risk of ovarian injury is related to the age of patient at the time of treatment, the cumulative dose of drug administered and the duration of treatment[18]. Temporary cessation of ovulation and menstruation result from damage to maturing follicles. Permanent effects occur when the number of surviving primordial follicles cannot sustain hormonal cyclicity. Amenorrhea frequently occurs in women over 40yrs (closer to their natural menopause) and is generally reversible in women less then 30yrs, thus making age the most important determinant of ovarian function.[15,19].

The fact that adjuvant chemotherapy will precipitate osteoporosis in breast cancer patients due to premature menopause is emphasized by Bruning et al, who observed 10% lower than age matched average BMD values in women who had become amenorrheic because of chemotherapy[20].

Endocrine Manipulation:

There are a number of endocrine treatment regimens in which a deliberate part of therapeutic strategy is premature ovarian insufficiency or the further reduction of circulating estrogen levels in women who have no ovarian function. Though the choice of endocrine agent is determined by multiple factors including,

menopausal status, stage of disease, prognostic factors and toxicity profile of the agent, these manipulations are associated with considerable long-term risk of osteoporosis[2, 21].

***Tamoxifen*:** This triphenyl derivative is the prototype of the Selective Estrogen Receptor Modulators (SERMs). At least two regions of the estrogen receptor are required for transcriptional activity: activating function-1, located near the amino terminus, and activating function-2, located within the ligand - binding domain. The ability to affect differentially the three-dimensional structure of the AF- 2 region after ligand binding has been suggested to be an important mechanism that contributes to the selective actions of the SERMs[22]. Depending on the tissue, tamoxifen exhibits a range of biologic activity from full estrogen antagonism to partial agonism. Despite acting as a partial estrogen agonist on the skeleton, it causes bone loss in the spine and hip in premenopausal patients because it has a weaker effect than the genuine estrogens[23, 24].

Other SERMs: Several other SERMs are currently being evaluated for prevention and treatment of breast cancer along with their role in maintaining bone health, including Raloxifene[25], Toremifene, Droloxifene, Idoxifene and Miproxifene[26]. Most of these agents in small studies have been found to improve upon bone health in osteoporotic postmenopausal patients, but the exact effect on bone

particularly in premenopausal ladies needs to be studied in large randomized controlled studies.

***Pure Antiestrogens*:** Another concept of endocrine manipulation is pure antiestrogens also known as Estrogen receptor down-regulators such as Fulvestrant have been shown to be an effective after tamoxifen failure. These antiestrogens are entirely free of partial agonist activity. They block transcriptional activity via the estrogen receptor both by preventing the binding of estrogen receptor to DNA and by reducing the number of estrogen acceptors. The effects of pure antiestrogens on the skeleton are as expected not very favourable. As they exhibit no agonist activity, an accelerated bone loss similar to that observed in early menopause is seen in younger women[27, 28].

Aromatase Inhibitors: In postmenopausal women, the majority of the residual levels of circulating estrogens are derived from androgens, which are secreted by the ovaries and the adrenal cortex and converted to estrogens in peripheral tissues, such as fat and muscle. The conversion to estrone and estradiol occurs via three hydroxylation steps which are catalyzed by the cytochrome P – 450 hemoprotein aromatase. Aromatase inhibitors are therefore effective inhibitors of residual estrogens in postmenopausal women. Both steroidal substrate analogs, ie, type I inhibitors (which inactivate the enzyme), and nonsteroidal competitive reversible analogs, ie type II inhibitors, such as anastrozole and letrozole, are available[29].

These inhibitors suppress estrogen levels by more than 95% in postmenopausal women.

The findings of Heshmati and Cummings now have proved beyond doubt that even minuscule gradients of estradiol is capable of influencing BMD and fracture particularly in the elderly. They found that despite such low levels, serum sex steroids have a positive effect on bone modulation and suppressing this result in about 15% bone resorption[30, 31].

Chemotherapy:

Chemotherapeutic agents are known to have hormone independent effects on bone health[2]. Cytotoxic drugs commonly used in treatment of breast cancer and have been known to have a negative affect on bone modulation are,

1. Cyclophosphamide.
2. Methotrexate.
3. Doxorubicin
4. Taxanes

Cyclophosphamide:

Treatment with cyclophosphamide has been associated with decrease in number of both osteoblasts and osteoclasts on the bone surface of the mandibular condyles and to cause osteopenia. These observations indicate that apart from its effects on the gonads, this agent may also have independent direct effects on bone metabolism[2].

Methotrexate:

Numerous therapy regimens in Oncology contain components that potentially have negative effects on bone metabolism independent of their effects on the sex hormone status. One such agent that has virtually been proven to have a causal role in osteopathy is methotrexate. The negative influence of methotrexate on bone mass seems to be due to an increase in bone resorption accompanied by inhibition of bone formation. As a result there is a massive uncoupling of bone turnover[32]. At cellular level it depletes reduced folates, which ultimately leads to an inhibition of DNA synthesis. This leads to reduced recruitment of osteoblastic cells from proliferative precursor cells, whereas it does not seem to affect osteoblast differentiation. Animal studies have shown that, methotrexate in a dose-responsive manner influences matrix mineralization[33, 34].

Some, albeit not all, studies have also shown an increase in bone resorption, as assessed by both increases in urinary hydroxyproline levels and histomorphometry. The lack of inhibitory effects on osteoclast numbers in contrast to osteoblast numbers may be due lower toxicity of osteoclast precursors to this agent, perhaps because of differences in the accumulation and exchange rate of this drug in different tissue compartments[35]. Several groups have reported severe osteoporosis with fractures in the course of long-term therapy with methotrexate. However, subclinical disease may be much more common. The osteopenia seemed

to be at least somewhat reversible after the drug was discontinued. It is not clear as to what extent adjuvant corticosteroid therapy played a role[2].

Doxorubicin:

Doxorubicin has been observed to cause a decrease in the trabecular bone volume in animal studies. The bone formation rate was also profoundly diminished by nearly 60%. Together, these findings suggest that doxorubicin has profound inhibitory effects on bone formation. The clinical relevance of these bone cell effects on human bone mass is unknown[2].

Taxanes:

Nabholtz JM, et al have reported that taxanes particularly docetaxel causes premature menopause when used in adjuvant setting in combination with cyclophosphamide and doxorubicin. However this effect was independently attributed to taxanes[36].

Ifosfamide, interferon-alfa and glucocorticoids are the other agents used in cancer therapy which are significantly associated with negative bone health.

Conventional risk factors:

Apart from the above mentioned breast cancer specific risk factors, women are also prone for and subsequently to fracture, due to the presence of conventional risk factors like any other individual. These factors include[6, 15, 37],

A. Nonmodifiable risk factors

1. Personal history of fracture as an adult.
2. History of fracture in first degree relative.
3. Female sex.
4. Advanced age.
5. Asian race

B. Potentially modifiable risk factors

1. Poor nutritional status.
2. Low body weight.
3. Low Calcium and Vitamin D intake.
4. Current cigarette smoking.
5. Alcoholism.
6. Inadequate physical activity.
7. Chronic diseases and Metabolic bone diseases.
8. Drugs like steroids, lithium, heparin etc.

Nutritional status:

Subjects with poor nutritional status will have deficiencies, which not only include calcium and vitamin D, but also essential amino acids, trace minerals etc. The end result is poor bone remodelling, in that bone resorption is more then new bone formation. As already known, risk of osteoporosis depends on peak bone mass which is achieved in adulthood, and if nutritional status is poor by any means, subsequently the peak bone mass attained is also sub-optimal[6, 14].

Calcium intake:

Apart from its role in attaining peak bone mass described above, calcium insufficiency induces secondary hyperparathyroidism, leading to bone resorption. Though this is a good short term measure to maintain calcium homeostasis, in long term it is detrimental to bone health. The recommended daily intake of calcium is 1000 to 1200mg for adults[38]. Similarly vitamin D deficiency also contributes to poor bone health and the daily recommended dose is 100 IU[39] in healthy general population and 400 to 800 IU in people at risk[37].

Physical inactivity:

Inactivity such as prolonged bed rest or paralysis results in significant bone loss. Evidence now suggests that chronic high level of physical activity has a

positive affect on bone mineral density. It has also been found that people involved in moderate exercise in childhood and through adulthood have lesser risk of fracture and better peak bone mass[6].

Low body weight:

Subjects with low body weight have high chances of poor bone health mostly due to suboptimal attainment of peak bone mass. Patients with poor nutritional status are likely to have low body weight and vice versa. In summary, poor bone health is the end result of poor nutritional intake leading on to low body weight and then finally ending up with osteoporosis and its consequences[6].

Chronic Diseases:

Various genetic and acquired diseases are associated with an increased risk of osteoporosis including thyrotoxicosis, hyperparathyroidism, cushing's syndrome, diabetes mellitus, acromegaly, chronic liver and renal diseases etc. Mechanisms that contribute to bone loss is an inter play of multiple factors including nutrition, reduced physical activity and use of medications.

Cigarette smoking:

Use of cigarettes over long period has detrimental effects on bone mass. These effects are mediated directly by toxic effects on osteoblasts and indirectly

by modifying estrogen metabolism. Smokers reach menopause 1 to 2 yrs earlier and are also prone for recurrent respiratory illness, frailty, and decreased exercise potential[6]. Similarly alcoholics have poor bone health due to direct effect on osteoblast, poor nutritional intake and the added risk of fall and fracture.

Management of bone health in breast cancer survivors:

Identification of high risk patients: Women with breast cancer diagnosis are at increased risk for osteoporosis and fracture. In one study by Kanis JA, et al it was reported that the presence of even localized breast cancers influenced fracture risk. Vertebral fracture risk was greater in breast cancer patients with resected, localized disease (odds ratio [OR], 4.7; 95% CI, 2.3 to 9.9) and 23 times greater in breast cancer patients with soft tissue metastasis without evidence of bone metastasis (OR, 22.7; 95% CI, 9.1 to 57.1) compared with women with no cancer[40].

However as per ASCO definition[37, 6], high risk is

1. All women with age >65 years
2. All women with age 60-64 years with one of the following
    a. family or personal history of fracture
    b. body weight <58 kg

c. any of the other risk factors described above

3. Postmenopausal lady of any age receiving aromatase inhibitors

4. Premenopausal lady with therapy associated premature menopause or having iatrogenic estrogen deficit status.

If the patient is at high risk for poor bone health, it is recommended to proceed with measurement of bone mineral density and define the status according to WHO definition described earlier.

Measurement of bone mass:

The techniques approved by FDA for estimating skeletal mass or density includes[6],

1. Dual energy X-ray absorptiomety (DXA)
2. Single-energy X-ray absorptiometry (SXA)
3. Quantitative computed tomography (CT) and
4. Ultrasound.

Dual energy X-ray absorptiomety:

DXA is a highly accurate X-ray technique and is the standard for measuring bone density in most cancers. Though it can be used for measurements of any skeletal site, clinical determinations are usually made from the lumbar spine and

hip. Portable DXA machines have been developed that measure the heel (calcaneus), forearm (radius and ulna), or finger (phalanges).

Computed Tomography: (CT)

CT is used primarily to measure the spine, and peripheral CT is used to measure bone in the forearm or tibia. Research into the use of CT for measurement of the hip is ongoing. The results obtained from CT are different from all others currently available since this technique specifically analyzes trabecular bone in vertebrae, eliminating posterior cortical elements of the spine, and can provide a true density (mass of bone per unit volume) measurement. However, CT remains expensive, involves greater radiation exposure, and is less reproducible.

Ultrasound:

Ultrasound is used to measure bone mass by calculating the attenuation of the signal as it passes through bone or the speed with which it traverses the bone. It is unclear whether ultrasound assesses bone quality, but this may be an advantage of the technique. Because of its relatively low cost and mobility, ultrasound is amenable for use as a screening procedure[44, 45]. In a study conducted by Kang et al, it was found that this method of measurement of BMD is comparable to DEXA[44] and has been approved by US FDA for measurement of BMD. The procedural details of using this machine is mentioned in the section Patients and Methods.

The hip is the preferred site of measurement in most individuals, since it predicts the risk of hip fracture, the most important consequence of osteoporosis, better than any other bone density measurement site. When hip measurements are performed by DXA, the spine can be measured at the same time. In younger individuals, such as perimenopausal or early postmenopausal women, spine measurements may be the most sensitive indicator of bone loss[6].

Osteoporosis prevention:

Most women with newly diagnosed breast cancer are at risk of osteoporosis either due to age or as a result of cancer treatment. Low BMD and history of fracture are two of the strongest fracture risk factors. One SD decrease in hip BMD is associated with a 2.6-fold increase in hip fracture risk[41]. The 5-year absolute risk of a vertebral fracture (*t* score = -2.5) is about 8%; this increases to about 15% over next 20 years. Women with a prevalent vertebral fracture are two to four times more likely to experience a new vertebral fracture and twice as likely to experience a hip fracture[42]. Thus as in any field of medicine, "Prevention is better than Cure".

Recommendations for osteoporosis screening:

The United States Preventive Services Task Force (USPSTF) recommends BMD screening for all high risk patients as mentioned above, but does not recommend routine screening for low risk subjects[43].

General principles of osteoporosis prevention and therapy:

Preventing osteoporotic fractures can be achieved by maximizing peak skeletal mass, preventing or slowing rates of bone loss, and preventing falls. Fundamental measures for bone health include adequate calcium intake (1,200 mg/d), and vitamin D intake (400 to 800 U), exercise, and avoidance of smoking. Women who should receive osteoporosis therapy include those with prior fragility fractures, as well as women with a BMD *t* score ≤-2.5[43]. Treatment of women without fractures but who have borderline low BMD (*t* score < -1.0) and other risk factors is controversial and should be decided on an individual basis.

The Osteoporosis Research Advisory Group (ORAG) has provided a comprehensive review of the randomized trials of osteoporosis therapies[46]. Vitamin D (hydroxylated), calcitonin, raloxifene, the bisphosphonates, etidronate, risedronate, and alendronate all reduced vertebral fractures with the strongest data supporting alendronate and risedronate. Only alendronate and risedronate significantly reduced nonvertebral fractures. The particular issues relevant to women with breast cancer are summarized in **Table 1**. In postmenopausal women,

tamoxifen had modest influence on BMD and fracture risk, but is not considered a stand-alone osteoporosis therapy. Raloxifene is approved for osteoporosis prevention and therapy exclusively in postmenopausal women but clinicians have reservations about its efficacy[47]. Other agents also influence fracture risk and include tibolone, strontium, and bisphosphonates clodronate, ibandronate, pamidronate, tiludronate, and zoledronic acid. Few recent studies including randomized trials have shown the beneficial effects of zoledronic acid[48], clodronate and ibandronate in reversing osteoporosis and improving BMD.

After the ORAG report was released, teriparitide[46], a synthetic parathyroid hormone, was approved for osteoporosis therapy. However, because this drug was associated with osteosarcoma development in animal studies, it is not recommended for use in women with diagnosed breast cancer[37].

Table 1. Therapies Available for Osteoporosis Prevention and Therapy: Approved by US FDA

Therapy	**Dosage**	**Common Side Effects**	**Issues for Use in Breast Cancer Patients**
FDA approved Bisphosphonates			
Alendronate	5 mg PO daily	Upper GI irritation, myalgias and arthralgias	None
Prevention and treatment	35 PO weekly		

	10 mg PO daily o		
	70 PO weekly		
Risedronate			None
Prevention and treatment	5 mg PO daily or		
	35 PO weekly		
Selective Estrogen Receptor Modulator			
Raloxifene			
Prevention and treatment	60 mg PO daily	Common: Hot flashes, leg cramps; rare: deep vein thromboses	Cross resistance with tamoxifen; not recommended after tamoxifen
Parathyroid Hormone (synthetic)			
Teriparitide	20 U SQ daily	Common: dizziness, leg cramps; rare: hypercalcemia	Not recommended; Should not be used in patients at increased risk of bone metastases or hypercalcemia (due to osteosarcoma development in animal models)
Estrogen plus progestin combination	Varies		
Five combination agents			
Prevention only		Common: breast tenderness, vaginal bleeding; life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with a breast cancer diagnosis when used for osteoporosis prevention
Estrogens			
Nine agents			
Prevention only	Varies	Common: breast tenderness, vaginal bleeding; life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with a breast cancer diagnosis when used for osteoporosis prevention
Calcium	1200 mg/d	Constipation, bloating, gas	None
Vitamin D	400–600 mg	None	None
Calcitonin nasal spray	200 U one nostril/day	Rhinitis	None
Abbreviations: FDA, Food and Drug Administration; PO, orally; SQ, subcutaneous; GI, gastrointestinal; CHD, coronary heart disease; PE, pulmonary embolism.			

Premenopausal therapy:

Regardless of receptor status, many premenopausal women are at risk of chemotherapy associated premature menopause, which results in rapid bone loss comparable to that seen with surgical oophorectomy (7.7% loss in lumbar spine

BMD in one report)[49]. Concurrent tamoxifen use in this setting may not be protective since some studies have suggested that tamoxifen itself is associated with loss of bone density in premenopausal women.

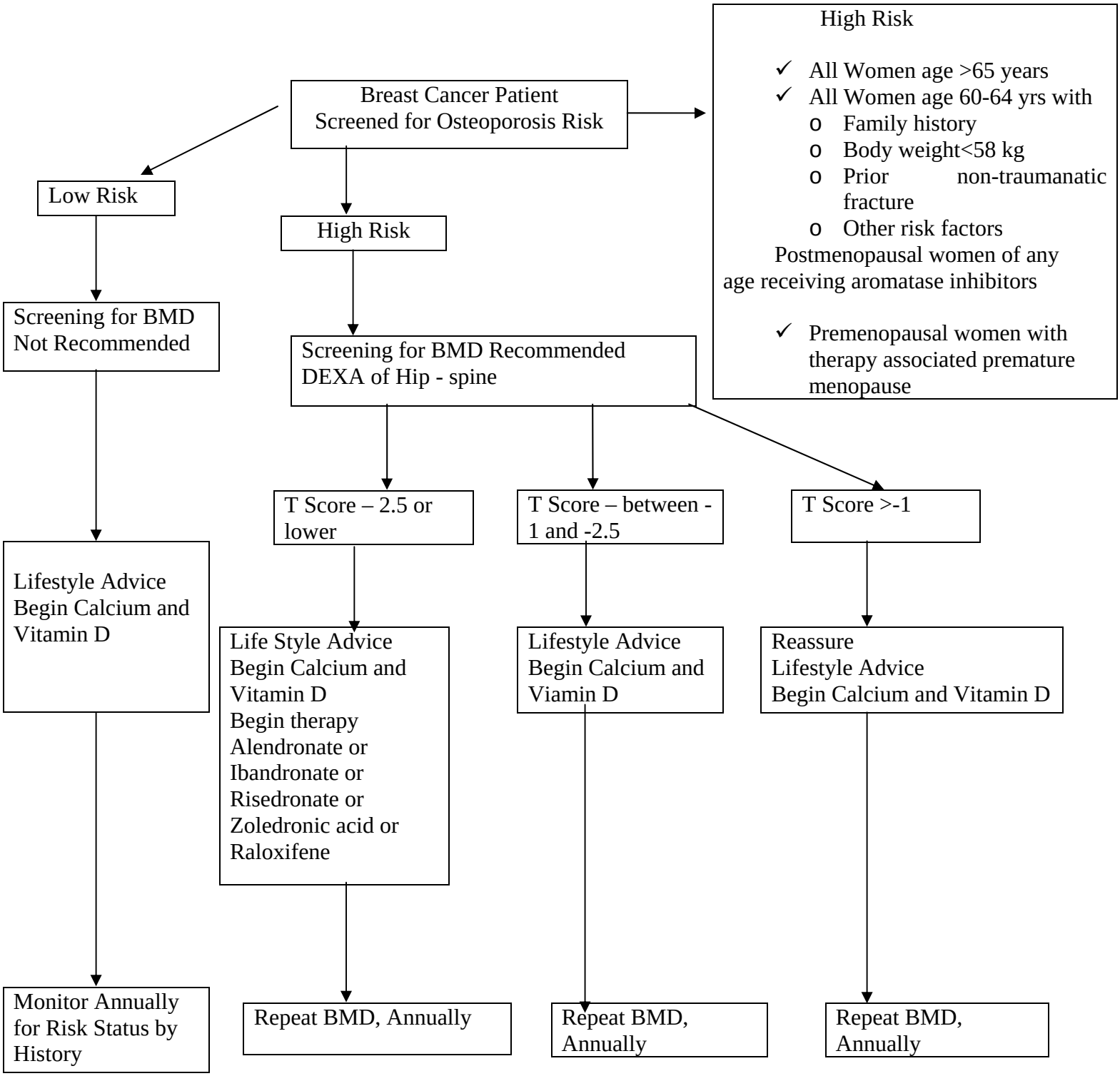
Bisphosphonates in combination with adjuvant therapy in breast cancer patients without bone metastases: The effect on BMD of bisphosphonates with hormonal or cytotoxic chemotherapy is being evaluated in comparative trials. In a small trial of 120 postmenopausal breast cancer patients without skeletal metastases, women were randomly assigned to one of two (SERMs), either tamoxifen or toremifene and, in a factorial design, had a second randomization to oral clodronate 1,600 mg daily or control (no bisphosphonate). At 2 years, clodronate together with a SERM markedly increased lumbar spine BMD by 2.9% (P = .001) while patients receiving the SERM alone did not significantly increase BMD[50].

For patients given adjuvant CMF chemotherapy, significantly less BMD loss occurred in women randomly assigned to oral clodronate compared with placebo[51]. Currently, there are only few reports on the efficacy of oral bisphosphonates for osteoporosis therapy. However ibandronate has been approved for this purpose. In a randomized trial of 52 patients, the bisphosphonate risedronate taken as 30 mg per day for 2 weeks followed by 10 weeks of no drug was shown to prevent bone loss in young women with breast cancer and premature chemotherapy induced menopause[52].

In a promising preliminary report, premenopausal breast cancer patients receiving goserelin plus anastrozole or goserelin plus tamoxifen were randomly assigned to the bisphosphonate zoledronic acid (4 mg IV q 6 months) or placebo. After 6 months, those receiving zoledronic acid had significantly higher lumbar spine BMD ($P < .0001$). Currently, there are no reports on the use of calcium and vitamin D in breast cancer patients free of bone metastases[53].

Bone health summary[37]*:* In otherwise healthy women, a strong body of evidence supports a strategy of early detection and therapy of osteoporosis. Similar recommendations can be applied to breast cancer patient management, as shown in Figure 1

Figure 1


Breast Cancer Patient
Screened for Osteoporosis Risk
High Risk
✓ All Women age >65 years
✓ All Women age 60-64 yrs with
o Family history
o Body weight<58 kg
o Prior non-traumanatic fracture
o Other risk factors
Postmenopausal women of any age receiving aromatase inhibitors
✓ Premenopausal women with therapy associated premature menopause
Low Risk
High Risk
Screening for BMD Not Recommended
Screening for BMD Recommended
DEXA of Hip - spine
T Score – 2.5 or lower
T Score – between -1 and -2.5
T Score >-1
Lifestyle Advice
Begin Calcium and Vitamin D
Life Style Advice
Begin Calcium and Vitamin D
Begin therapy
Alendronate or
Ibandronate or
Risedronate or
Zoledronic acid or
Raloxifene
Lifestyle Advice
Begin Calcium and Viamin D
Reassure
Lifestyle Advice
Begin Calcium and Vitamin D
Monitor Annually for Risk Status by History
Repeat BMD, Annually
Repeat BMD, Annually
Repeat BMD, Annually

***Future directions*:**

Treatment related bone loss:

Irrespective of bone metastases, it is possible that all early stage breast cancer patients could benefit from bisphosphonates in the form of preservation of bone density. Adjuvant aromatase inhibition in postmenopausal patients and ovarian suppression in premenopausal patients are the subjects of ongoing studies.

The final report of the Austrian Breast Cancer Study Group randomized trial of zoledronic acid in premenopausal women treated with hormonal therapy is eagerly anticipated.

The international pharmaceutical company-sponsored Zometa/Femara Adjuvant Synergy Trial study is an open-label, randomized, multicenter study evaluating the use of zoledronic acid in the prevention of cancer treatment-related bone loss in postmenopausal breast cancer patients receiving letrozole as adjuvant therapy[54]. The International Breast Cancer Intervention Study II comparing anastrozole to placebo in women at high risk of developing breast cancer, and tamoxifen to anastrozole in ductal carcinoma in situ, has subprotocols including a bisphosphonate examining the effects of risedronate on prevention of bone loss associated with anastrozole. CALGB protocol 79809 is a phase II trial of

intravenous zoledronic acid for the prevention of bone loss among localized breast cancer patients with chemotherapy-induced ovarian failure.

Osteoclast targeted therapies:

Additionally, nonbisphosphonate compounds that interfere with bone metabolism are under investigation in breast cancer patients with bone metastases. Agents of interest include anti-RANK ligand pathway-targeted therapy, and anti-parathyroid hormone-related peptide antibodies[37].

PATIENTS AND METHODS

PATIENTS AND METHODS

The present study was conducted at Cancer Institute (WIA), Chennai. A total of 70 subjects were included in this prospective case control study, with each group consisting of 35 subjects.

Inclusion criteria:

For Patients:

1. Patients diagnosed as carcinoma breast based on histopathology of invasive carcinoma between 1993-2005.
2. Patients treated with multimodality therapy.
3. Patients younger than or equal to 30 years at the time of diagnosis.
4. Patients who have completed 2 years of follow up.
5. Patients who underwent castration or had chemotherapy related amenorrhoea for more than 12 months[56].

For Controls: An equal number of age and sex matched healthy controls.

Exclusion criteria:

1. Patients with metastatic disease.
2. Patients who continue to menstruate.
3. Patients with other risk factors for osteoporosis like steroid intake, rheumatoid arthritis, chronic renal failure and metabolic bone disease.

Methodology:

Thirty five patients of breast cancer who fulfilled the inclusion and exclusion criteria were registered into the study as cases. These patients had received multimodal therapy as per the Institute protocol. These individuals were subsequently assessed as per the protocol of the study. This includes recording their present age, duration of follow up, height, weight, type of adjuvant treatment, duration of castration/amenorrhoea and measurement of Bone Mineral Density. All the individuals also underwent baseline investigations with haemogram, renal function tests, liver function tests, blood sugar level and serum calcium.

Similarly age and sex matched healthy controls were chosen from the attendees accompanying the patients and were subjected to above mentioned tests including BMD.

Measurement of Bone Mineral Density[44]***:***

BMD was measured using Ultrasound Bone Densitometer CM-100 manufactured by Furuno Electric Co. LTD Japan[45], with following specifications,

- Measurement Site: Heel (calcaneus)
- Measurement method: Ultrasound pulse penetration
- Measuring parameter: Speed of sound
- Ultrasound frequency: 500 kHz

- Measurement time: approx 10 seconds.

Procedure: The CM-100 is a bone densitometer using ultrasound to measure speed of sound (SOS) in the heel and contributed to screening and diagnosis of osteoporosis. First the gel was applied to heel and the foot was positioned on the foot rest on machine. The cylinder was aligned so that the foot set properly on the foot rest. After pressing the start key, over the next 10 seconds the result was printed based on speed of sound.

- Normal if SOS > 1514m/s
- Osteopenia if SOS is between 1514m/s and 1479m/s
- Osteoporosis if SOS is < 1479m/s[44].

Statistical Analysis:

Descriptive statistical analysis has been carried out on the basis of analysis of the results of the study. Chi-square and Fisher Exact test were used to test the level of significance of BMD between the groups. Pearson Correlation was used to find the significance of study parameters with BMD.

The statistical software SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used to analyse data.

OBSERVATIONS AND RESULTS

RESULTS AND OBSERVATIONS

Table 1: Distribution of age at diagnosis among cases

Age (years)	*Number*	*%*
25-26	5	14.3
27-28	8	22.9
29-30	22	62.9
Total	35	100.0
Mean ± SD	28.57 ± 1.74	

Table 2: Distribution of present age among cases and controls

Age(years)	*Cases*		*Controls*	
	No	*%*	*No*	*%*
Up to 30 years	2	5.7	2	5.7
31-35 years	23	65.7	20	57.1
36-40 years	8	22.8	12	34.3
41-45 years	2	5.7	1	2.9
Total	35	100.0	35	100.0
Mean ± SD	34.31±3.02		34.60 ±3.07	

Table 3: Duration of follow up among cases

Duration of follow-up	*Number*	*%*
< 3 years	5	14.3
3–6 years	20	57.14
> 6 years	10	28.57
Mean ± SD	5.69 ± 3.10	

Table 4: Distribution of duration of AE* therapy

Duration of AE(years)	*Number*	*%*
2.00 - 3.00	7	20.0
3.01 - 4.00	8	22.9
4.01 - 5.00	11	31.4
Completed 5 yrs	9	25.7
Total	35	100.0
Mean ± SD	4.34 ± 1.57	

* AE-Antiestrogen

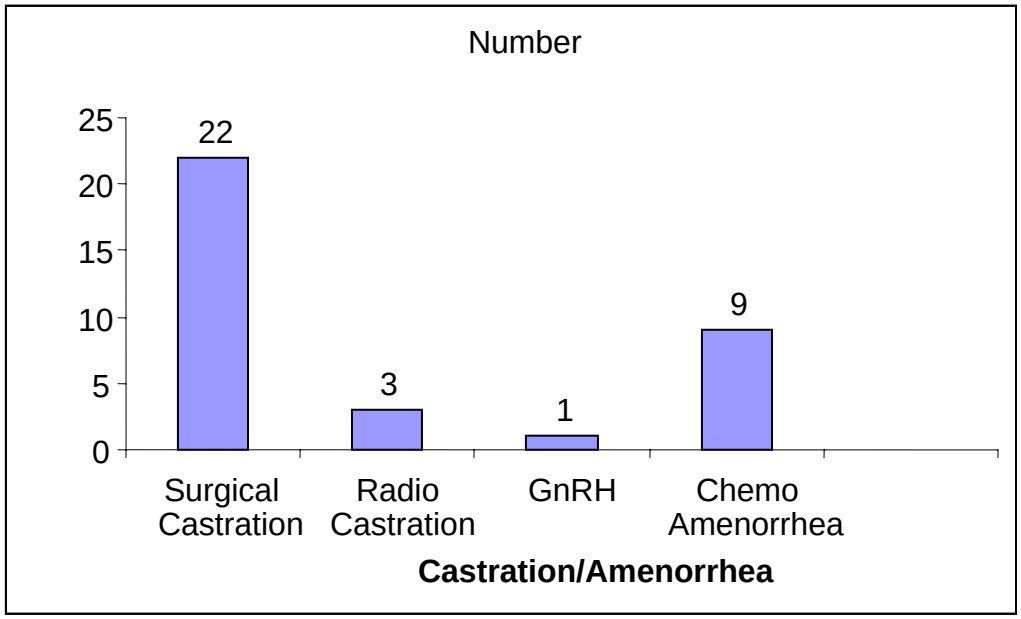


Figure 1: Distribution of patients with Castration and Chemo amenorrhea

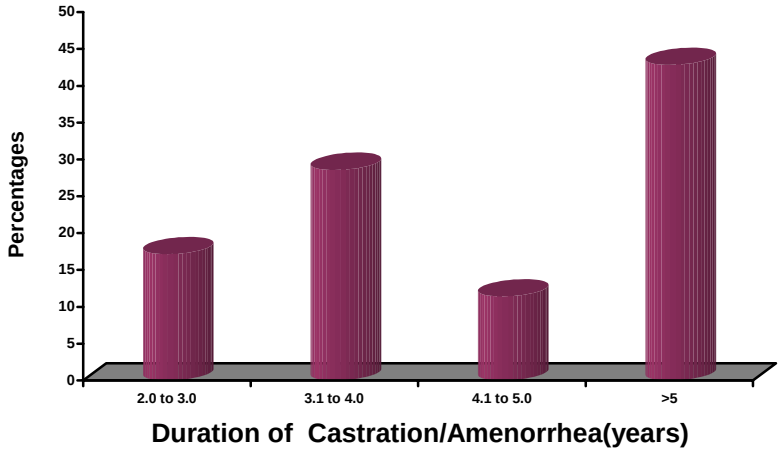


Figure 2: Duration of follow up after Castration and Chemo amenorrhea

Table 5: Distribution of Bone Mineral Density (BMD) among cases and controls

BMD(t-score)	***Cases***		***Controls***		***P values***
	No	***%***	***No***	***%***	
<-2.5	7	20.0	1	2.8	0.055
-2.5 to -1.1	15	42.9	5	14.3	0.008
>-1.0	13	37.1	29	82.9	<0.001
Total	35	100.0	35	100	
Mean ± SD	-1.41 ± 1.25		-0.22 ±0.98		

Table 6: Distribution of BMI among cases and controls

BMI(kg/m^2)	***Cases***		***Controls***	
	No	***%***	***No***	***%***
Up to 20	2	5.71	3	8.57
21-25	18	51.43	18	51.43
26-30	11	31.43	11	31.43
31-35	4	11.43	3	8.57
Total	35	100.0	35	100.0
Mean ± SD	25.11 ± 3.53		24.66 ±3.56	

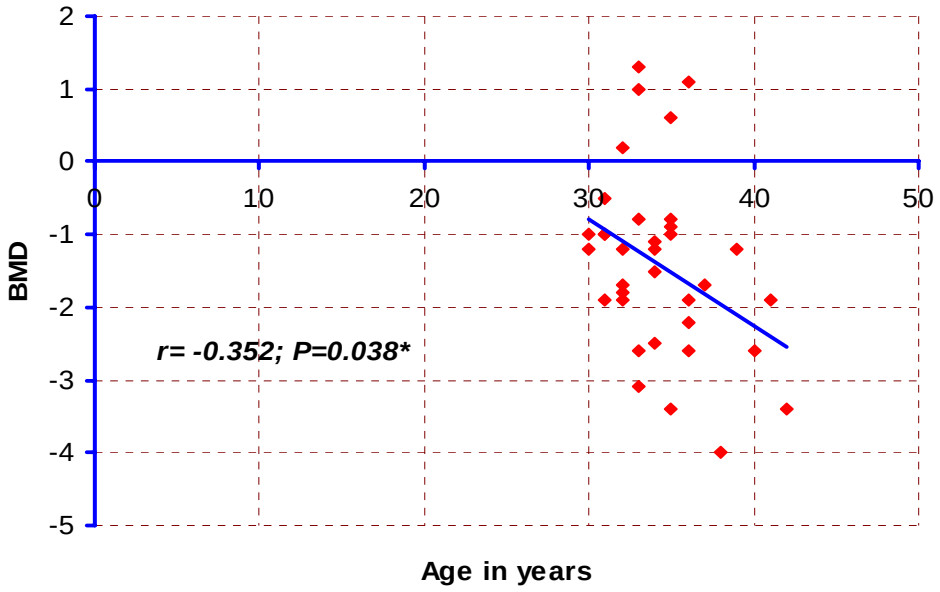


Figure 3: Correlation between BMD and Age at follow up

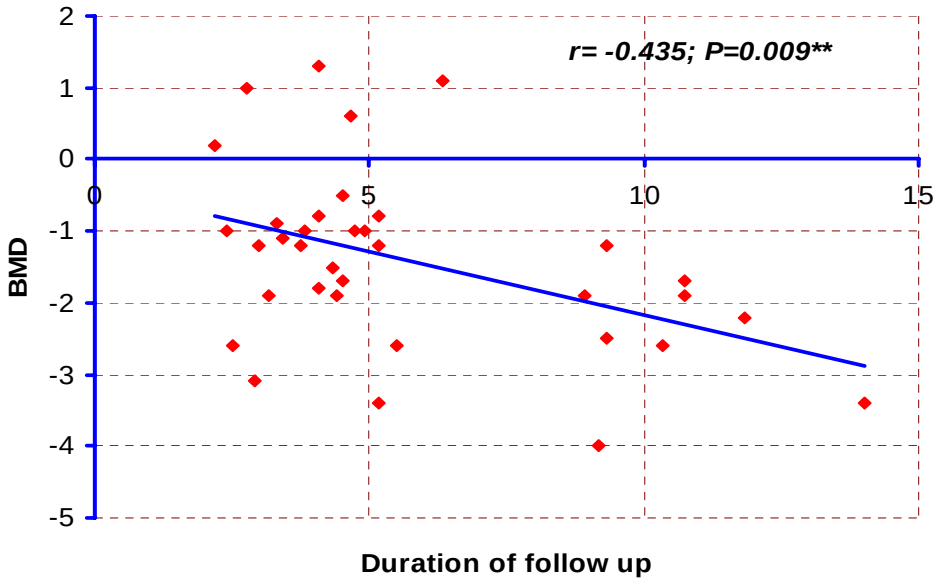


Figure 4: Correlation between BMD and Duration of Follow up:

Table 7: Comparison of BMD among chemotherapy schedules

BMD(t-score)	*FAC**		*CMF***		*P values*
	No	*%*	*No*	*%*	
<-2.5	2	13.33	5	25.0	
-2.5 to -1.1	7	46.67	8	40.0	
>-1.0	6	40.0	7	35.0	
Total	15	100.0	20	100	
Mean ± SD	-1.35±1.05		-1.46±1.4		0.80

* Adriamycin, Methotrexate, 5-flurouracil

**Cyclophosphamide, Methotrexate, 5-flurouracil

Table 8: Comparision of BMD among patients with castration and chemo amnorrhea.

BMD(t-score)	*Castration*		*Chemoamenorrhea*		*P values*
	No	*%*	*No*	*%*	
<-2.5	5	19.23	2	22.22	
-2.5 to -1.1	12	46.15	3	33.33	
>-1.0	9	34.62	4	44.45	
Total	26	100.0	9	100	
Mean ± SD	-0.77±1.82		-1.63±0.94		0.25

Thirty five patients of Breast Cancer and an equal number of matched healthy controls were included in the study.

Age at Diagnosis (Table 1): The mean age at diagnosis of patients was 28.57 years and majority of the patients were in the age group of 29-30 years when a diagnosis of carcinoma of breast was made.

Present age (Table 2): The present age of patients (age at time of BMD) was statistically similar to the age of controls and hence both the groups were comparable.

Duration of follow up (Table 3): The median duration of follow up was 4.5 years, with majority of patients having a follow up in the range of 3 years to 6 years.

Duration of Antiestrogen(AE) therapy (Table 4): The median duration of antiestrogen therapy was 4.42 years with 57.1% of them taking it for more than 4 years. Tamoxifen was the only AE used among all cases.

Distribution of patients with Castration and Chemo amenorrhea (Figure 1): Of the thirty five patients, 22 (62.85%) has surgical castration in the

form of bilateral salphingo oopherectomy, 3 (8.58%) had radiocastration, while only one patient was on GnRH. Nine patients (25.72%) had chemo amenorrhea. Of the 15 patients on FAC, 3(20%) developed chemo amenorrhea and of the 20 patients on CMF 6 (30%) developed chemo amenorrhea. However this difference was not statistically significant.

Duration of followup after Castration & Chemoamenorrhea(Figure2): The mean duration of follow up was 5.56 years (± 3.17) with almost 55% of patients having a follow up of 4 years and beyond.

Bone Mineral Density (Table 5): The mean BMD was -1.41 among cases which falls into Osteopenic range while it was -0.22, among controls which was normal. This difference was highly statistically significant. Nearly 63% of patients had poor bone health as compared to only 17% among controls.

Correlation between BMD and Age at follow up (Figure 3): There was a statistically significant inverse correlation between age of the patient and BMD (P-0.03) which means more the age of the patient, lower is the BMD. The r value was -0.35 by Pearson correlation.

Correlation between BMD and Duration of Follow up (Figure 4): As the duration of follow up increased patients tend to have poorer bone health and

this correlation was also statistically significant with P-value of 0.009 and r value of -0.43. Of the patients with more than 5 years of follow up (n=15) 6 (40%) had osteoporosis and 7 (46.67%) had osteopenia.

BMD among the chemotherapy schedules (Table 7): Although there was a trend towards poor bone health in patients receiving CMF as compared to FAC, this was not statistically significant.

Comparison of BMD among patients with castration and chemo amenorrhea (Table 8): There was no statistically significant difference in Bone Mineral Density between Castrated and Chemo amenorheic patients with a P-value of 0.25.

DISCUSSION

DISCUSSION

In our study of bone mineral density among young patients of breast cancer, we tried to look at the bone health of these young patients. Of the 35 cases, 7 (20%) were found to be osteoporotic and another 15 (42.9%) were osteopenic, this when compared to controls had only one (2.8%) subject with osteoporosis and 5 (14.3%) subjects with osteopenia. Our results not only revealed that, nearly 63% of patients had poor state of bone health but also that bone mineral density worsened with the duration of follow up.

The detailed discussion of the observations and results in our study are as follows.

Demographic profile:

Age: The mean age of patients at diagnoses was 28.57 ± 1.74, since the study was limited to patients with less than 30yrs age at diagnoses. As found in various studies and in Surveillance, Epidemiology, and End Results (SEER) data and a study by Yeole BB et al in India, the incidence of breast cancer in the age group of 20-29yrs is less than 1% and that of 30-39 yrs is 6.5% to 10%[55, 57].

The mean age of the patients at the time of last follow up (when BMD was done) was 34.31±3.02 years. Two patients (5.7%) were more than 40 yrs while

nearly 65.7% (23) of were in the range of 31-35yrs. The mean age among controls was 34.31±3.02 yrs and both the groups were statistically comparable. The importance of age in these young patients who receive adjuvant therapy is that, it perfectly correlates with chemotherapy induced amenorrhea. In a study by Shapiro, et al they found that more the age of the patients, lesser is the chance for retaining menstrual function[49] and amenorrhea is always almost irreversible in women over age 30 years[19]. In addition, patients with increasing age, tend to have natural bone loss resulting into a poorer bone mass[14].

Duration of follow up:

The mean duration of follow up among cases was 5.69 ± 3.10 yrs with 10 patients (28.57%) being followed for more than 6 yrs after the end of protocol with multimodality therapy. As per a study done by Fogelman I, Blake GM, et al as the period after adjuvant therapy increases more and more patients become amenorrheic. In there study the incidence of amenorrhea was 60.5%, 69.4% and 76.5% at 6 months, 2years and 3years respectively after adjuvant therapy[14].

Duration of Anti-estrogen therapy:

The mean duration of Anti-estrogen therapy in our study was 4.34 ± 1.57, with 9 (25.7%) patients completing the scheduled five years of adjuvant tamoxifen

and another 11 (31.4%) patients had taken for more than 4 years. As per institute protocol, all the patients were on tamoxifen only. While tamoxifen prevents bone loss in postmenopausal women, it has opposite effect in premenopausal females. According to a study by Leena V, Inkeri E, et al, at 3 yrs follow up premenopausal women on tamoxifen had a mean bone loss of -4.6% while postmenopausal females had a stable BMD or reduced bone loss as compared to controls[58]. However in our study there was no statistically significant correlation between BMD and duration of anti-estrogen therapy.

Castration and Chemotherapy induced amenorrhea:

Out of 35 patients in our study, 22 (62.85%) patients had surgical castration, 3 had radio castration, one had medical castration with GnRH and 9 (25.72%) had chemo amenorrhea. 20% of patients on FAC and 30% of patients on CMF developed chemo amenorrhea, but this difference was not statistically significant. As reported by Shapiro CL, Manola J, et al 63% to 85% of patients on CMF and more than 50% of patients on FAC develop permanent chemo amenorrhea[49]. Almost all the patients with amenorrhea lasting for more than 12 months never regained menstrual functioning[56].

Duration of follow up after Castration and Chemo amenorrhea:

The mean duration of follow up after patient had iatrogenic menopause was 5.56 years (± 3.17) with almost 55% of patients having a follow up of 4 years and

beyond. The relevance of follow up after patients had iatrogenic ovarian failure is stressed in a study by Cummings SR et al, who reported that castrated patients, if osteoporotic, have a 8% increased risk of vertebral fractures at 5 years which increases to 15% at 20 years[41]. In our study of the 15 patients with more than 5 yrs of follow up, 6 (40%) were osteoporotic and 7 (46.67%) were osteopenic. Thus nearly 87% of the study population post 5 yrs of iatrogenic menopause was at risk of fragility fractures.

Bone Mineral Density (BMD) among cases and controls:

The mean BMD among cases was -1.41 ± 1.25 and that among controls was -0.22 ±0.98 and this difference was statistically significant. Twenty percent of patients (N=7) were osteoporotic as compared to 2.8% (N=1) among controls. Similarly, 42.9% (N=15) cases and 14.3% (N=5) of controls were osteopenic. All these differences are statistically significant. According to a study in India by Sharma et al, the incidence of osteopenia among young adults between 35-44 yrs is 15.51%[59]. Similarly, Lin JD reported that incidence of osteopenia in the age group of 21-30 yrs is 8% and in 31-40 yrs is 10%, while the incidence of osteoporosis is 1% in both groups[60]. Leena V et al have reported that on an average, 7% of BMD is lost within one year and this rate is similar in patients with chemo amenorrhea as well as surgical castration[58].

BMI and weight among cases and controls:

Body mass index and weight were statistically similar between cases and controls. In our study, neither BMI nor weight had correlation with bone mineral density. Few studies have reported significant correlation between weight and BMI. Lesser the weight (<58 kg), more is the risk of osteoporosis and subsequent fractures[6, 37].

Correlation between BMD and Age at follow up:

In our study there was a statistically significant correlation between age of the patient and bone mineral density (P-value of 0.03). As the age of patient increased, there was worsening of bone density. Fogelman I, Blake GM, et al, have reported that BMD loss at lumbar spine was -4.5% to -8.2% at end of one year, -6.5% to -10.5% at end of two years and -6.2% to -7.2% in the third year[14]. Thus, as in our study with each increasing year, there was loss of BMD. Similarly Richelsen et al have reported that oophorectomized women had bone mineral density similar to postmenopausal women 20 years older and this detoriated with further follow up[11].

Correlation between BMD and Duration of Follow up:

In our study there was a significant statistical correlation between fall in bone density with increasing duration of follow up as well as increasing duration of ovarian insufficiency. In a study reported in Osteoporosis International[14] there

was 20% decline in bone mass over a period of 10 yrs and this was contributed by both iatrogenic menopause as well as age related changes like decreased physical activity, poor nutritional state, coexistence of co-morbid conditions and use of medications which can erode bone mass.

Comparison of BMD among chemotherapy schedules:

In our study, the mean BMD was -1.35±1.05 among 15 patients who received FAC as compared to -1.46±1.4 among 20 patients who received CMF. A total of 9 patients (60%) in the FAC sub-group had poor bone density as compared 13 (65%) in the CMF arm. Though there was a trend towards negative bone health among CMF patients, this did not reach statistical significance. As per the literature, patients with CMF have 30% to 80% more risk of becoming amenorrheic as compared to anthracycline based chemotherapy[15] and hence have a higher risk of becoming osteoporotic. In an article by Johannes P and Diel IJ, cyclophosphamide causes osteoporosis indirectly by inducing ovarian failure while methotrexate has direct effect on bone which has been described as methotrexate osteopathy. Role of anthracyclines in humans to affect bone metabolism is not clear[2].

Comparison of BMD among patients with castration and chemo amenorrhea:

Among the 26 patients who underwent castration, 17 (65.38%) had poor bone health as compared to 5 (55.55%) patients who had chemotherapy induced

loss of menstrual function. The mean BMD between these two groups was not statistically significant. Leena V, Elomaa I et al have reported that the decrease in BMD during first year is similar to that of surgically castrated patients[58]. However Fogleman I, et al, have reported that in patients with medical castration (GnRH) the fall in BMD is much steep as compared to chemo amenorrhea arm, however BMD improved significantly once GnRH was stopped, while it continued to detoriate in chemotherapy arm[14]. An interesting hypothesis was proposed by Charles LS et al, that women who experience chemotherapy-induced ovarian failure develop rapid and highly significant decrease in BMD in the spine and femur, detectable with in 6 months post treatment. This is akin to surgical or medical ovarian ablation with rapid decrease in estrogen level, rather than natural menopause where estrogen levels wax and wane and decline over several years[15].

CONCLUSION

CONCLUSION

- ✓ The bone mineral density among young patients with breast cancer was significantly poorer as compared to matched controls.
- ✓ Bone mineral density continued to fall with increasing age of the patient and increasing duration of ovarian insufficiency.
- ✓ There was no significant difference in BMD between patients who underwent castration or had chemo amenorrhea.
- ✓ There was no significant difference in BMD among patients with different chemotherapy schedules.
- ✓ Antiestrogens did not significantly affect bone health of patients.
- ✓ Interventions to reduce bone loss as well as long-term follow up studies are needed in women undergoing castration or chemo amenorrhea.
- ✓ Routine and regular assessment of the osteoporosis risk is warranted in the management of women with breast cancer.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Althius MD, Dozier J M, Anderson WF, et al. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol 2005; 34: 405-412.

2. Johannes Pfeilschifter, Diel JI. Osteoporosis due to cancer treatment: Pathogenesis and management. J Clin Oncol 2000; 18: 1570-1593.

3. Cooper C. The crippling consequences of fractures and their impact on quality of life. Am J Med 1997; 103: 12s-19s.

4. Schurch MA, Rizzoli R, Mermillod B, et al. A prospective study on the economic aspects of fracture of proximal femur. J Bone Miner Res 1996; 11: 1935-1942.

5. Barr RD, Simpson T, Webber CE, et al. Osteopenia in children surviving brain tumors. Eur J Cancer 1998; 34: 873-877.

6. Robert L, Cosman F. Osteoporosis. In: Kasper DL, Braunwald E, Fauci AS, et al (Eds). In: Harrison's Principles of Internal Medicine, New York: Mc Graw Hill; 2005: 2268-72.

7. Genant HK, Engelke K, Fuerst T, et al. Non-invasive assessment of bone mineral and structure: State of art. J Bone Miner Res 1996; 11: 707-730.

8. Kanis JA, Melton LJ, Christiansen C, et al. The diagnosis of Osteoporosis. J Bone Miner Res 1994; 9: 1137-1141.

9. Moy B, Paul EG. Bone Integrity in survivors of Breast Cancer. In: Ramaswamy G (Eds). In: American Society of Clinical Oncology Education Book, Alexandria; 2007: 529-533.

10. Jilka RL : Cytokines, bone modeling, and estrogen deficiency: A 1998 uptodate. Bone. 1998; 23: 75-81.

11. Richelson LS, Wahner HW, Melton LJ III, et al: Relative contribution of aging and estrogen deficiency to postmenopausal bone loss. N Engl J Med 1984; 311: 1273-1275.

12. Cann C, Martin M, Genant H, et al: Decreased spinal mineral content in amenorrheic women. JAMA 1984; 251: 626-629.

13. Johansen J, Riis B, Hassager C, et al: The effect of gonadotropin-releasing hormone agonist analog (nafarlin) on bone metabolism. J Clin Endocrinology Metab 1988; 67: 701-70

14. Fogleman I, Blake GM, Blamey R, et al. Bone mineral density in premenopausal women treated for node positive early breast cancer with 2 yrs of goserelin or 6 months of CMF. Osteoporos Int 2003; 14:1001-1006.

15. Charles LS, Judith M, Meryl L. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early stage breast cancer. J Clin Oncol 2001; 19:3306-3311.

16. Plowchalk DR, Mattison DR. Phosphoramide mustard is responsible for the ovarian toxicity. Toxicol Appl Pharmacol 1991; 107: 471-481.

17. Ataya K, Moghissi K. Chemotherapy-induced premature ovarian failure: Mechanism and prevention. Steroid 1989; 54:607-626.

18. Heshmati HM, Khosla S, Robins SP, et al. Endogenous residual estrogen levels determine bone resorption even in post menopausal women. J Bone Miner Res 1997; 12:121 (suppl).

19. Gradishar WJ, Schilsky RL. Effects of cancer treatment in reproductive system. Crit Rev Oncol Hematol 1988; 82: 153-171.

20. Bruning PF, Pit MJ, Long-Bakker M, et al. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. Br J cancer 1990; 61:308-310.

21. Catherino WH, Jordan VC. A risk-benefit assessment of tamoxifen therapy. Drug safety 1993; 8:381-397.

22. Mitlak BH, Cohen FJ: Selective estrogen receptor modulators. Drugs 1999; 57: 653-663.

23. Powles TJ, Hickish T, Kanis JA, et al. Effect of tamoxifen on bone mineral denity measured by dual energy Xray absorptiomentry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996; 14:78-84.

24. Garrett TJ, Vahdat LT, Kinne DW. Systemic adjuvant therapy of breast cancer. J surg Oncol 1997; 64: 167-172.

25. William CW, Hyman BM, Solin LJ, et al. Malignant tumors of breast. In: DeVita VT, Samuel H, Steven A, et al (Eds). In: Cancer Principles and Practice of Oncology, Philadelphia: Lippincott & Wilkins 2005: 1427-1428.

26. Howell A, Downey S, Anderson E. New endocrine therapies for breast cancer. Eur J Cancer 1996; 32A: 576-588.

27. England GM, Jordan VG: Pure antiestrogens as a new therapy for breast cancer. Oncol Res 1997; 9:397-402.

28. William CW, Hyman BM, Solin LJ, et al. Malignant tumors of breast. In: DeVita VT, Samuel H, Steven A, et al (Eds). In: Cancer Principles and Practice of Oncology, Philadelphia: Lippincott & Wilkins 2005: 1456-1459.

29. Hamilton A, Piccart M. Third-generation non-steroidal aromatase inhibitors: A review of their clinical benefits in the second line hormonal treatment of advanced breast cancer. Ann Oncol 1999; 10: 377-384.

30. Heshmati HM, Khosla S, Robins SP, et al. Endogenous residual estrogen levels determine bone resorption levels even in late postmenopausal women. J Bone Miner Res 1997:12 :121(suppl 1).

31. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among the older women. N Engl J Med 1998; 339:733-738.

32. Wheeler DL, Vander Griend RA, Wronski TJ, et al. The short and long term effects of methotrexate on rat skeleton. Bone 1995; 16:215-221.

33. Scheven BA, Veen MJ, Damen CA, et al. Effects of methotrexate on human osteoblast in vitro: Modulation by 1,25 dihydroxyvitamin D3. J Bone Miner Res 1995; 16:874-880.

34. Van der Veen MJ, Scheven BA, Van Roy JL, et al. In vitro effects effect of methotrexate on human articular cartilage and bone- derived osteoblast. Br J Rheumatol 1996; 35: 342-249.

35. Suzuki Y, Nakagawa M, Masuda C, et al. Short term low dose methotrexate ameliorates abnormal bone metabolism and bone loss in adjuvant induced arthiritis. J Rhematol 1997; 24: 1890-1895.

36. Nabholtz JM, Pienkowski T, Mackey J, et al. phase III trial comparing TAC in the adjuvant treatment of node positive breast cancer: interim analysis of the BICRG 001 study. Proc Am Soc Clin Oncol 2002; 21: 36a (abstr141).

37. Bruce EH, James NI, Gracy C, et al. American Society Of Clinical Oncology 2003 update on the role of biphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003; 21:4042-4057.

38. Neer RM. Effects of parathyroid harmone on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344:1434.

39. Dawyer J. In: Braunwald E, Facci AS, Kasper DL, et al (Eds). In: Harrison's Principles of Internal Medicine Newyork: Mc Graw Hill 2001: 451-55.

40. Kanis JA, McCloskey EV, Powles T, et al. A high incidence of vertebral fracture in women with breast cancer. Br J cancer 1999; 79: 1179-1181.

41. Cummings SR, Bates D, Black DM. Clinical use of bone densiometry: scientific review. JAMA 2002; 288: 1889-1897.

42. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3 year randomized clinical trial. Multiple Outcomes of Raloxfene Evaluation (MORE) Investigators. JAMA 1999; 282:637-45.

43. US preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002; 137: 526-28.

44. Kang C, Speller R. Comparison of ultrasound and dual energy X-ray absorptiometry measurements in the Calcaneus. Br Journal of Radiology 1998; 71: 861-67.

45. Kishimoto H, Yoh K, Ohta H, et al. Normative data and cut-off values determined using Quantitative Ultrasound CM-100 in Japanese women. Osteoporosis Japan 2003; 11: No 2.

46. Cranney A, Guyatt G, Griffith L, et al. Meta-analysis of therapies for postmenopausal osteoporosis IX: Summary of meta-analysis of therapies for postmenopausal osteoporosis. Endocr rev 2002; 23: 570-78.

47. Fisher B, Dignam J, et al. Five Vs more than five yrs of tamoxifen for node negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 2001; 93: 684-90.

48. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low BMD. N Engl J Med 2002; 346:653-61

49. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early stage breast cancer. J Clin Oncol 2001; 19: 3306-3311.

50. Saarto T, Vehmanen L, Elomaa I, et al. The effect of clodronate and antiestrogens on bone loss associated with oestrogen withdrawl in postmenopausal women with breast cancer. Br J Cancer 2001; 84:1047-51.

51. Saarto T, Blomqvist C, Valimaki M, et al. Chemical castration induced by adjuvant CMF causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. J Clin Oncol 1997; 15: 1341-47.

52. Delmas PD, Balena R, Confravreux E, et al. Biphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double blind, placebo controlled study. J Clin Oncol 1997; 15: 955-62.

53. Gnant M, Hausmaniger H, Samonigg H, et al. Changes in BMD caused by anastrazole or tamoxifen in combination with goserelin (+/- zoledronate) as adjuvant treatment for hormone receptor positive premenopausal breast

cancer: results of randomized multicentre trial. Breast Cancer Res Treat 2002; 76:531(suppl).

54. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol 2006; doi:10.1200/JCO.2005.05.3744.

55. Yeole BB, Kurkure AP. An epidemiological assessment of increasing incidence and trends in breast cancer in Mumbai and other sites in India, during the last two decades. Asian Pac Cancer Prev 2003; 4:51-56.

56. Marvin LM, Rena VS, Larry IL. Gonadal Dysfunction. In: DeVita VT, Samuel H, Steven A, et al (Eds). In: Cancer Principles and Practice of Oncology, Philadelphia: Lippincott & Wilkins 2005: 2563-2565.

57. Surveillance, Epidemiology, and End Results (SEER): Cancer Statistics review, 1973-1988. Bethesda MD; July 1991.

58. Leena V, Inkeri E, Carl B, et al. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. J Clin Oncol. 2006; 24:675-680.

59. Sharma S, Tandon V, Mahajan A, et al. Preliminary screening of osteoporosis and osteopenia in urban women from Jammu using calcaneal QUS. Indian J Med Sci 2006; 60: 183-89.

60. Lin JD, Chen JF, Chang HY, et al. Evaluation of bone mineral density by quantitative ultrasound of bone in 16862 subjects during routine health examination. BJR 2001; 74: 602-06.

PROFORMA

PROFORMA

NAME - WEIGHT - kg

AGE - HEIGHT - cm

OP. NO - BMI - kg / m^2

DIAGNOSIS - BMD -

STAGE -

DATE OF DIAGNOSIS -

AGE AT DIAGNOSIS -

TREATMENT RECEIVED

1. CHEMOTHERAPY - CMF / FAC / OTHERS
2. SURGERY - BCS / MRM
3. RADIOTHERAPY - GY

TREATMENT COMPLETED ON

ANTIESTROGENS – TAMOXIFEN / ANASTRAZOLE / LETROZOLE

1.) RECEIVED FROM TO

2.) DURATION

H/O FRACTURE - YES / NO IF YES AGE -

FAMILY HISTORY OF FRACTURE – YES / NO IF YES, AGE -

CASTRATION DONE – YES / NO IF YES

(Surgical / radiation / medical)

1. AGE 2. Date

CHEMO AMENORRHEA - YES / NO

INVESTIGATIONS

1. HEMOGLOBIN -

2. TOTAL COUNT -

3. PLATELETS -

4. RANDOM BLOOD SUGAR -

5. BLOOD UREA -

6. SERUM CREATININE -

7. TOTAL BILIRUBIN -

8. SGOT -

9. SGPT -

MEDICATIONS

1. CALCIUM SUPPLEMENTS - YES / NO

2. OCP - YES / NO

3. BISPHOSPHONATES - YES / NO

DIET

1. EGG - YES / NO

2. MILK – YES / NO